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From Diabetes to Diabetic Complications: Role of Autophagy*

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[Abstract] Diabetes and its complications reduce quality of life and are life-limiting. At present, diabetes treatment consists of hypoglycemic agents to control blood glucose and the use of insulin-sensitizing drugs to overcome insulin resistance. In diabetes, autophagy is impaired and thus there is poor intracellular environment homeostasis. Pancreatic β-cells and insulin target tissues are protected by enhancing autophagy. Autophagy decreases β-cell apoptosis, promotes β-cell proliferation, and alleviates insulin resistance. Autophagy in diabetes is regulated by the mammalian target of rapamycin (mTOR)/adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) pathway and others. Autophagy enhancers can likely be used as a treatment for diabetes and its complications. This review examines the evidence linking autophagy to diabetes.
Key words: autophagy; diabetes; diabetic complications; mechanism

Diabetes mellitus (DM) is a chronic condition that affects the way of the body processing glucose. Although DM is increasingly better managed with diet, exercise and medication, DM prevalence is estimated to rise to 10.2% in 2030 and 10.9% in 2045[1]. DM can be classified into two main types: Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is an autoimmune disease that is induced by auto-antibody and results in β-cell damage[2]. T2DM is a metabolic disorder caused by insulin resistance (IR)[3]. Both types cause hyperglycemia. DM can cause a range of complications that include diabetic nephropathy (DN), diabetic central neuropathy, diabetic cardiomyopathy (DC), and diabetic retinopathy (DR)[4].

Autophagy is a cyclical process facilitated by lysosomes, which plays a critical role in cellular metabolism, intracellular environment homeostasis, and function of organelles, such as mitochondria and endoplasmic reticulum. It can be divided into macro-autophagy, micro-autophagy, and chaperone-mediated autophagy[5]. The autophagy process consists of three stages: initiation, extension, and degradation. The key molecules in the initiation stage are UNC51-like kinase 1 (ULK1) complex and the Bcl-2-interacting myosin-like coiled-coil protein (Beclin1). Under the external environment's influence (such as starvation and rapamycin), the upstream mammalian target of rapamycin (mTOR) inactivates ULK1 phosphorylation and initiates autophagy. ULK1 phosphorylates Beclin1, causing it to recruit Vps34, Vps15 and Atg14L to form complexes. Then, double FYVE-containing protein 1 (DFCP1), WIPI2 (a PI3P-binding effector protein), and other autophagy-related (Atg) genes are recruited. The autophagy extension process includes two ubiquitination steps. LC3-I is conjugated to phosphatidylethanolamine (PE) to become LC3-Ⅱ and Atg12 conjugates to Atg5 and Atg16L to form a ubiquitin complex. After the autophagosome extension is completed, it is hydrolyzed together with lysosomes to maintain homeostasis *in vivo*[6–8]. Beclin1, LC3-Ⅰ/LC3-Ⅱ ratio or LC3-Ⅱ, and ATG-related genes are positive observation indexes that are increased in autophagy activation. P-mTOR and autophagic substrate P62 are negative observation indexes that are increased in autophagy inhibition[9, 10].

Autophagy is involved in insulin homeostasis regulation[11]. It can inhibit β-cell apoptosis and promote β-cell proliferation to treat diabetes, but Atg expression is reduced in DM patients[12]. The function of autophagy is also influenced by various factors that include cytokine interaction and that are regulated by other signaling pathways or protein molecules (fig. 1). Cytokines are involved in immunity, inflammation, and

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diabetes development. Abnormal pro-inflammatory cytokines secretion (such as TNF-α, IL-6) and decreased inflammatory mediators (such as C3, IL-4, IL-10) are causative of IR[13]. Autophagy is an intrinsic cellular defense mechanism of the immune response[14]. Mitogen-activated protein kinase (MAPK) and c-Jun NH2-terminal kinase (JNK) pathway play an important role in autophagy and T2DM occurrence[15]. The MAPK family includes JNK, extracellular signal-regulated kinase (ERK) and p38MAPK, which can regulate Atg gene expression[16]. Adenosine 5′-monophosphate (AMP)-activated pro-tein kinase (AMPK) also plays an important role in autophagy. AMPK is widely distributed throughout human tissues and its main function is to ensure the normal function and energy homeostasis of mitochondria and strictly control inflammation, autophagy, and apoptosis. AMPK imbalance contributes to metabolic and mitochondrial dysfunction-related diseases[17]. Activation of the AMPK/sirtuin1 (SIRT1)-forkhead box proteins O1 (FoxO1) pathway enhances autophagy and alleviates oxidative stress[18]. Mitochondrial dysfunction in islet cells causes insulin secretion disorder, and timely removal of damaged mitochondria can improve β-cell quality. Vesicle-associated membrane protein 7 (VAMP7), a vesicular trap protein that mediates specific membrane fusion during intracellular transport, is elevated in diabetic models and promotes autophagosome formation to maintain mitochondrial homeostasis and β-cell insulin secretion[19]. VAMP7 is located in the Atg9a resident vesicle of the recycling endosome, and it participates in autophagosome formation and enhances autophagosome-lysosome fusion by interacting with fusion synapsin 17 (STX17)[20].

This review summarizes autophagy's role

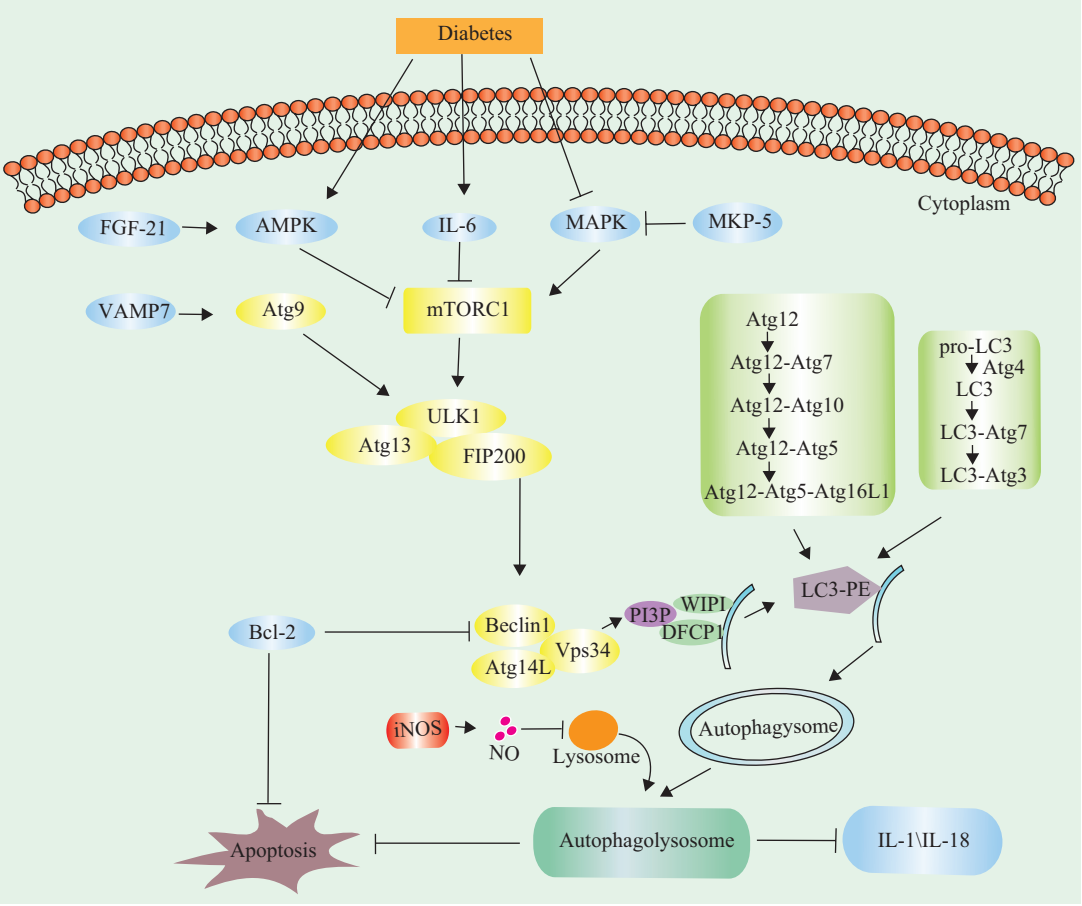

Fig. 1 Molecular mechanism of autophagy in diabetes mellitus development

Diabetes directly or indirectly activates mTORC1 to inhibit autophagy and activates autophagy through related molecule regulation. (1) FGF-21 activates AMPK to inhibit mTORC1 and initiate autophagy; (2) IL-6 activates autophagy by inhibiting mTORC1 signaling; (3) MKP-5 inhibits mTORC1 activation by MAPK to initiate autophagy; (4) VAMP7 binds with Atg9 to promote autophagosomes and lysosomes fusion; (5) Bcl-2 can inhibit apoptosis and Beclin1 involved in autophagy; (6) iNOS produces NO, which damages the function of lysosome and affects the fusion of autophagosome and lysosome. AMPK: AMP-activated protein kinase; Bcl-2: B-cell lymphoma gene 2; DFCP1: double zinc finger structural protein; FGF-21: fibroblast growth factors 21; FIP200: family interacting proteins; IL-6: interleukin 6; IL-18: interleukin 18; MAPK: mitogen-activated protein kinase; MKP-5: mitogen-activated protein kinase phosphatase-5; PI3P: phosphatidylinositol-3-phosphate; ULK1: UNC51-like kinase complex 1; VAMP7: vesicle-associated protein 7; Vps34: a precursor of the phosphatidylinositol 3-kinase family; WIPI: PI3P binding effector protein

and mechanism in DM progression and diabetic complications. It will provide a theoretical basis for DM prevention and treatment.

1 EFFECT AND MOLECULAR MECHANISM OF AUTOPHAGY IN DIABETES

Autophagy has been widely studied in both *in vitro* and *in vivo* models of diabetes (table 1). The main pathological diabetic changes are β-cell apoptosis and IR. Autophagy balance plays an important role in the development of diabetes (fig. 2).

1.1 Interaction between Cytokines and Autophagy

Cytokines activate the AMPK/ULK1 pathway to inhibit mTOR and stimulate autophagy activity in an endoplasmic reticulum (ER) stress-dependent manner[21]. Autophagy then inhibits the expression of inflammatory cytokines.

Table 1 Autophagy and diabetes development

	Model	Result	Conclusion	References
Animals	C57BL/6J	LC3↓, P62↑	HFD impairs autophagy.	[34]
	SD	LC3↑, P62↓	IH activates autophagy to protect β-cells.	[36]
	C57BL/6J	Atg5↓, LC3↓	HFD and STZ impair autophagy.	[40]
	SD	LC3↓, Beclin1↓, P62↑	HFD and STZ impair autophagy.	[43]
	C57BL/6	GTT↑, ITT↑, p-AKT↓	Atg3 and/or Atg16L1 KO induces insulin resistance.	[45]
	C57BL/6J	p-AMPK↓, p-mTOR↑, P62↑	HFD-induced inhibition in hepatic autophagy in mice through AMPK/mTOR	[51]
	ob/ob	LC3↓, Beclin1↓, Atg5↓, Atg7↓	Obesity downregulates hepatic autophagy.	[52]
Cells	INS-1E	AMPK↑, mTOR↓, LC3↓, P62↑	IL-1β and IFN-γ stimulate the early steps of autophagy while blocking the autophagic flux, which aggravate β cell apoptosis.	[21]
	INS-1	LC3↑, P62↑	Glucolipotoxicity increases basal autophagic activity but impairs autophagic flux.	[35]
	INS-1	LC3↑, P62↓	IH induces autophagy activation in INS-1 cells.	[36]
	Rin-m5f, 293A	LC3↑, Beclin1↑, P62↓	MKP-5 improves autophagy inhibition in lipotoxicity-induced Rin-m5f cells.	[37]
	Min6, INS-1	LC3↑, P62↑, Atg5↑	Lipotoxicity leads to a defect in the lysosomal degradation of β-cells.	[103]

1.1.1 Effect of Cytokines on Autophagy IL-6 plays an important role in the connection between innate immune response and adaptive immune response and participates in inflammation, IR, and β-cell dysfunction[22]. It inhibits oxidative stress and protects β-cells through the promotion of insulin secretion and maintenance of the redox state of mouse islets[23]. Studies have shown that IL-6 reduced oxidative stress and autophagy in the hippocampal CA1 region, thus inhibiting neuronal inflammation and apoptosis[24]. *In vitro* and *in vivo*, IL-6-induced autophagy by janus kinase (JAK)/signal transducer activation and activator of transcription (STAT) signaling pathway (fig. 1) attenuates myocardial ischemia-reperfusion injury[25]. Increases of p-STAT3(tyr705) and activation of STAT3 promoted autophagy and inhibited β-cells apoptosis after INS-1 cells were treated with IL-6[26]. Another study found that IL-6 inhibited the combination of antioxidant factor, NF-E2-related factor 2 (Nrf2), and its endogenous inhibitor, Kelch-like ECH-associated protein 1 (KEAP1), increased Nrf2 content and reduced reactive oxygen species (ROS). β-cells with IL-6 receptor knockout were more susceptible to oxidative damage and diabetes. Phospho-p62 then bound to KEAP1 in β-cells to induce degradation of KEAP1 through autophagy. IL-6 induces autophagy and reduces pancreatic β-cell oxidative stress, ameliorating diabetes[27].

Complement component C3 is the most abundant complement component in serum, which is mainly synthesized by macrophages and the liver. It plays an important role in the classical and bypass activation complement pathways. It is the pivot between immunity and other functions[28]. Studies have reported that C3 was highly expressed in pancreatic β-cells and was bound to autophagy-related protein Atg16L1. INS-1 cells were supplemented with chloroquine and further with C3. LC3-Ⅱ expression was found to be increased. Conversely, LC3-Ⅱ expression was not changed in $C3^{-/-}$ INS-1 cells, suggesting that C3 played an important role in inducing autophagy and C3 absence led to autophagosome maturation disorder or LC3-Ⅱ degradation. Thus, C3 expression is critical for normal β-cell autophagy[29].

1.1.2 Effect of Autophagy on the Expression of Cytokines The NLRP3 inflammasome is an innate immune response that promotes IL-1 and IL-18 secretion by activating caspase-1 and contributes to diabetes development[30]. NLRP3 and IL-1β mRNA expression is significantly increased in wound macrophages of diabetic patients. In THP-1-derived macrophages, high glucose (HG) leads to impaired autophagy, increased ROS production, activated NLRP3 inflammasome, and increased IL-1 secretion.

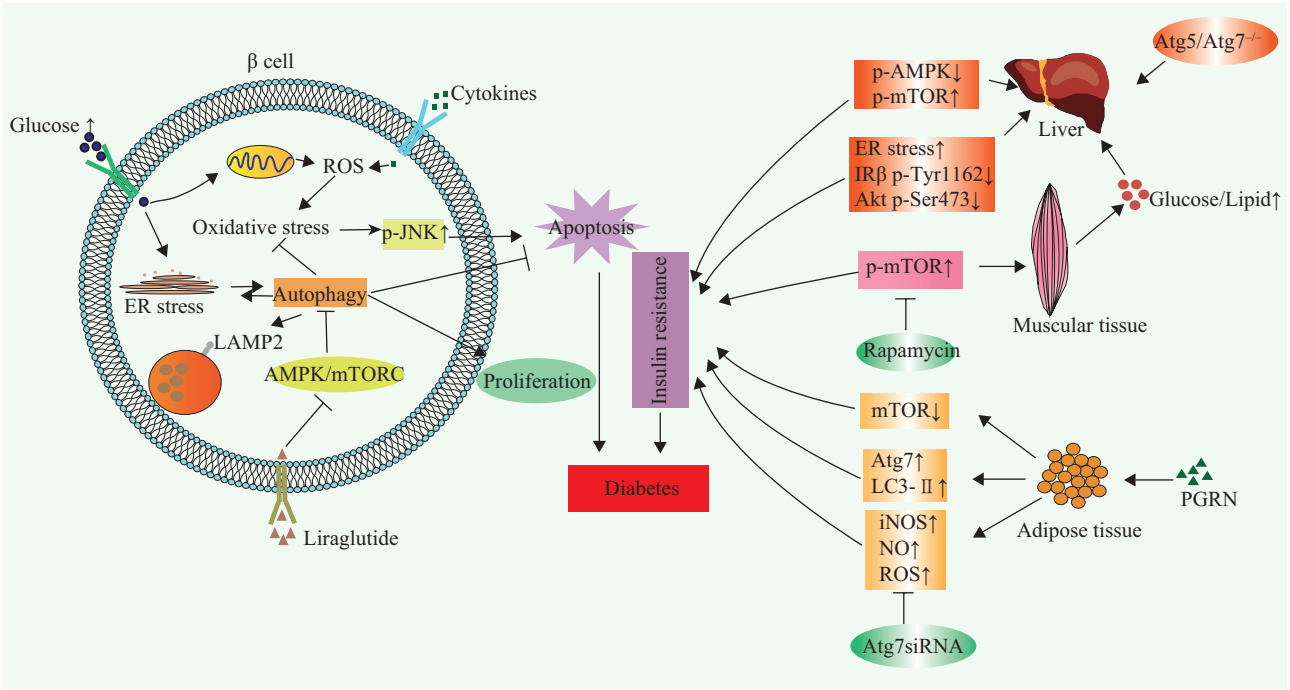

Fig. 2 Autophagy and diabetes development

(1) β-cells are stimulated by oxidative stress and ER stress, and oxidative stress activates JNK to induce β-cell apoptosis. Autophagy inhibits oxidative stress to reduce JNK activation, thereby inhibiting β-cell apoptosis. Liraglutide activates autophagy through mTOR inhibition to reduce β-cell apoptosis and promote proliferation. (2) p-mTOR expression in liver and skeletal muscles increased, autophagy was impaired, and IR appeared after high-glucose (HG) and high-fat or autophagy-related gene knockout. The expression of mTOR in adipose tissues decreased and autophagy increased after PGRN treatment, and IR occurred. Akt p-Ser473: phosphorylation of serine 473 site of insulin-sensitive kinase; AMPK: adenosine 5′-monophosphate (AMP)-activated protein kinase; Atg: autophagy-related genes; ER stress: endoplasmic reticulum stress; iNOS: inducible nitric oxide synthase; IRβ p-Tyr1162: phosphorylation of insulin receptor β subunit tyrosine at 1162; LAMP2: lysosomal associated membrane protein 2; LC3: microtubule binding protein 1A/1b light chain 3; mTOR: mammalian target of rapamycin; NO: nitric oxide; p-JNK: phosphorylated c-Jun N-terminal kinase; PGRN: progranulin; ROS: reactive oxygen species

Enhanced autophagy reduces the number of damaged mitochondria that produce ROS, thus inhibiting the activation of NLRP3 inflammasome and alleviating the inflammatory state[31]. Atg16L1-deficient macrophages produce large amounts of inflammatory cytokines (IL-1β and IL-18) after lipopolysaccharides (LPS) stimulation[32]. These results suggest that autophagy is negatively correlated with inflammatory cytokines.

1.2 β-cell Apoptosis and Regeneration

The number of β-cells in T1DM patients is <10% of that in unaffected people and insulin secretion is insufficient. β-cell dysfunction and apoptosis are important factors for T1DM development[33]. Reducing β-cell apoptosis and promoting β-cell regeneration are two ways to improve T1DM. Studies have shown that autophagy plays an important role in the process of β-cell apoptosis and regeneration[34]. Autophagy deficiency increased damaged mitochondria and oxidative stress accumulation, which then damaged lysosomes to promote β-cell apoptosis[21]. β-cell survival is improved by relieving the impairment in autophagic flux and stimulating autophagy[35]. Intermittent hypoxia (IH) promotes pancreatic β-cell apoptosis but promotes autophagy with rapamycin-alleviated IH-induced apoptosis[36]. This is similar to that reported for palmitic acid/glucose-induced β-cell apoptosis that can be inhibited by enhancing autophagy[37]. MKP-5 is a lipid metabolism upstream MAPKs regulator that negatively regulates MAPKs through direct dephosphorylation. MKP-5 overexpression protects against β-cell apoptosis and dysfunction, and lack of MKP-5 increases lipid toxicity[37]. Under the effect of glucose palmitic acid, MKP-5 overexpression inhibits caspase-3 and caspase-9 upregulation and PARP-1 expression in MIN6 cells. This reduces the expression of glucose regulatory protein-94 and X-box binding protein-1, to inhibit mitochondrial apoptosis, alleviate ER stress and decrease β-cells apoptosis caused by glucolipotoxicity[38]. The JNK, ERK, and P38MAPK phosphorylation levels in RIN-PC cells were increased after treatment with glucose palmitic acid. Overexpression of MKP-5 inhibited MAPK activation, decreased p-JNK, ERK, and P38MAPK, increased LC3-Ⅱ expression, and decreased P62 expression. JNK, ERK, and P38MAPK phosphorylation levels increased after MKP-5 knockout, suggesting that MKP-5 promoted autophagy by inhibiting JNK and p38MAPK pathways to inhibit the glucose palmitic acid-induced β-cells inflammatory response and oxidative stress, apoptosis, and β-cell dysfunction[37].

Rno-circRNA-008565 inhibits JNK expression and promotes autophagy of rat islet β-cells, suggesting that the gene level could also affect the autophagy of β-cells through the MAPK signaling pathway[39]. Autophagy was also enhanced by increased p-AMPK and decreased p-mTOR in diabetes treatment[40].

Autophagy is also very important for β-cell regeneration. Studies have found that after a high-fat diet (HFD), intermittent fasting stimulated β-cell regeneration depending on an intact autophagy-lysosome pathway[34]. The Atg5 up-regulation expression enhanced autophagy and promoted proliferation of β-cell[40], and the enhancement of β-cell proliferation was mediated by AMPK/mTOR signaling[41].

1.3 IR

IR is one of the key pathophysiological processes involved in T2DM[42]. Some studies have shown that autophagy played an important role in regulating the normal β cells and insulin target tissue function (such as liver, skeletal muscle, and adipose tissue)[5]. Rapamycin improved IR and hepatic steatosis in diabetic rats by activating autophagy[43]. Autophagy was reduced in H_9C_2 cells treated with lipid-carrying proteins, resulting in IR. After rapamycin addition, insulin sensitivity was restored[44]. In Atg3 knockout mice fed with HFD, both glucose tolerance and insulin tolerance were impaired, suggesting that autophagy damage led to mitochondrial dysfunction, adipose inflammation, and systemic IR[45]. Studies have shown that fibroblast growth factor (FGF21) regulated insulin sensitivity and glucose homeostasis. FGF21 reduced lipid accumulation and cell death caused by lipotoxicity through increasing p-AMPK and decreasing p-mTOR[46, 47]. Also, lysosomal dysfunction led to obesity-related hepatic IR[48]. VAMP7 maintained Atg9a function in pancreatic β-cells, promoted autophagosome formation and alleviated diabetes. In VAMP7 knockout mice and MIN6 cells, autophagosome formation was reduced, dysfunctional mitochondria were not cleared effectively, and adenosine triphosphate (ATP) production and insulin secretion were impaired[49].

1.3.1 Liver The liver is the metabolic center and an inflammatory environment that promotes steatosis development, which is a hepatic IR characteristic feature[50]. The expression of p-AMPK was significantly decreased and p-mTOR was increased in the liver of HFD mice, suggesting that HFD inhibited autophagy production in mouse liver tissue. Autophagy is promoted by increasing AMPK phosphorylation, which improves IR and glucose intolerance in the liver[51]. In hepatocellular models with Atg5 or Atg7 deficiency, increased ER stress results in a significant decrease of insulin-stimulated p-Tyr1162/1163 of insulin receptor β subunit (IRβ) and Akt pSer473, leading to serious IR. This was also demonstrated by suppressing Atg7 expression in the liver tissue of lean mice using an adenovirus-mediated approach *in vivo*[52]. The expression levels of autophagic markers Atg7, Beclin1, and LC3-II/LC3-I ratio were reduced in ob/ob mouse liver and p-AMPK was reduced. Increased p-mTOR was observed in the ob/ob group and sitagliptin significantly ameliorated IR by activating autophagy via AMPK/mTOR signaling pathway in ob/ob mice[53]. It has been found that taurine could ameliorate inorganic arsenic-induced IR through PPARγ-mTORC2 signaling activation and subsequently inhibit hepatic autophagy in mouse liver and HepG2 cells[54]. Inducible nitric oxide synthase (iNOS), an inflammation marker, can be activated in obesity to produce NO and impair lysosomal function. In obese mice, iNOS inhibited transcription factor EB (TFEB) or Atg7 and decreased insulin sensitivity. Knocking out iNOS improved systemic glucose and insulin homeostasis, TFEB activity, and nuclear translocation[55]. S-nitroglutathione reductase (GSNOR) played a key regulatory role between autophagy and inflammation. In GSNOR-deficient mice, obesity increased the nitriding lysosome and mitochondria stress and S-nitroso protein expression in the liver, impairing autophagy, resulting in IR. S-nitrosoylation of JNK, IKK and Bcl-2 disrupted autophagy and liver overexpression of GSNOR enhanced autophagy and improved glucose tolerance of HFD-fed mice[56, 57].

1.3.2 Skeletal Muscle In a cohort study, it was found that the Atg5 and LC3 Ⅱ expression in the skeletal muscles of T2DM patients was inhibited and autophagy body formation was impaired, resulting in IR in skeletal muscles[58]. Glucose tolerance was impaired in T2DM mice, which caused a decrease in insulin sensitivity and IR appearance in skeletal muscles[59]. Mice with long-term weightlifting training have promoted muscle adaptation and insulin sensitivity with simultaneous enhancement of autophagy and mTOR pathways[60]. Dysregulation of the mTORC1-autophagy pathway decreased glucose uptake, contributing to hyperandrogenism-induced skeletal muscle IR. Dihydromyricetin improved skeletal muscle IR by inducing autophagy via AMPK signaling pathway activation[61]. Other studies have shown that exercise significantly increased LC3 Ⅱ/LC3 Ⅰ and Beclin1 in the skeletal muscle of T2DM mice, while P62 and p-mTOR/mTOR significantly decreased, contributing to the improvement of insulin sensitivity in skeletal muscle. The mechanism was that exercise ameliorated IR through increasing skeletal muscle cells autophagy by binding to G protein-coupled receptor 43[62].

1.3.3 Adipose Tissue Adipose tissue is the center of fat accumulation, energy consumption, glucose and insulin metabolism, and hormone regulation, which

plays an important role in maintaining systemic energy metabolism homeostasis. Adipose tissue of insulin-resistant humans exhibited excessive lipolysis and impaired lipogenesis that led to cytokines release and lipid metabolites[63]. Studies have shown progranulin-mediated adipose IR and exhibited adipose autophagy, as well as attenuated insulin signaling via mTOR pathway inhibition. Furthermore, blocking tumor necrosis factor receptor 1 (TNFR1) restored impaired insulin sensitivity by progranulin[64]. Studies have also found that iNOS and ER stress inhibition both increase autophagy and protect against IR in adipocytes[65]. Atg7siRNA inhibited ER stress and improved the insulin sensitivity of adipocytes[66]. Autophagy inhibition can alleviate IR in adipose tissue. Other studies reported that the number of autophagosomes in T2DM adipocytes significantly increased to promote cell survival. Diabetic adipocytes showed a dependence on autophagy to maintain intracellular ATP concentration, as evidenced by ATP concentration reduction after autophagy inhibition. In addition, autophagy was enhanced and the number of lipofuscin granules in the adipocytes of T2DM patients was significantly reduced[67]. Therefore, autophagy's role in adipose tissue IR remains controversial.

2 EFFECT AND MOLECULAR MECHANISM OF AUTOPHAGY IN DIABETES COMPLICATIONS

When diabetes develops, it can cause damage to organs, particularly the kidney, brain, heart, and retina. Autophagy plays a significant role in diabetic complications (table 2).

Table 2 Autophagy and diabetic complications

Diabetic complication	Model		Result	Conclusion	References
Diabetic nephropathy	Animal	C57 BL/6J	GFP-LC3↓, P62↑	Exacerbation of DN in podocyte-specific Atg5-deficient mice	[72]
		C57 BL/6J	LC3-Ⅱ↓, P62↑	Deletion of Atg5 accelerates DN.	[73]
		SD	LC3↓, P62↑, p-mTOR↑	Autophagy decreases in DN.	[78]
	Cell	Podocyte cell	GFP-LC3↓, P62↑	Insufficient autophagy in cultured podocytes stimulated with serum from DN patients	[72]
		Proximal tubule cell	LC3-Ⅱ↓, GFP-LC3↓, ULK1↓	HG suppresses autophagy and downregulates ULK1 in proximal tubule cells.	[74]
Diabetic central neuropathy	Animal	C57B/L	LC3-Ⅱ↓, p-mTOR↑	Autophagy decreases in the hypothalamus of diabetic mice.	[81]
		SD	LC3-Ⅱ/ LC3-Ⅰ↓, Beclin1↓	Diabetes compromises neuronal cell autophagy.	[80]
		C57BL/6	LC3-Ⅱ↑, Beclin1↑, P62↓,	Autophagy is induced in DM mice.	[82]
		C57BL/6J, KKAy	LC3↓, Beclin1↓, P62↑	Decreased autophagy of hippocampal neurons in T2DM mice	[24]
		C57BL/6J	LC3-Ⅱ↑, p-mTOR↓, p-AMPK↑	Autophagy activation alleviates diabetes-induced hippocampal neuronal injuries.	[85]
	Cell	PC12	LC3-Ⅱ↓, p-mTOR↑	Lipotoxicity suppresses autophagy and cell viability in PC12 cells.	[81]
		Hippocampal neurons	Cleaved caspase-3↑	Inhibition of autophagy aggravates hippocampal primary neurons apoptosis.	[82]
		HT22	LC3↓, Beclin 1↓, P62↑	Decreased autophagy of HT22 cells exposed to HG	[24]
	Animal	SD	LC3-Ⅱ↓, Atg5↓, Atg7↓	Cardiac autophagy reduces in DM.	[88]
		C57BL/6	LC3↓, P62↑	Autophagy inhibition in the hearts of the diabetic mice	[90]
Diabetic cardiomyopathy	Cell	H9c2	LC3-Ⅱ/LC3-Ⅰ↑, P62↓	HG upregulates autophagy in H9c2 cells.	[87]
		H9c2	LC3-Ⅱ↓, Beclin1↓	Inhibition of autophagy accelerates apoptosis of H9c2 cells treated with HG.	[90]
		H9c2	LC3Ⅱ↓, Atg5↓, Beclin-1↓	HG significantly decreases autophagy of H9c2.	[92]
		SD	LC3Ⅱ↑, Atg3↑, Atg5-Atg12↑, Beclin1↑	Hyperglycemia induces autophagy in the retinas.	[100]
Diabetic retinopathy	Animal	SD	LC3↑, Beclin1↓, p- mTOR↓	Autophagy is disordered in the diabetic retina.	[101]
	Cell	Müller cell	Beclin1↓, P62↑	HG decreases Müller cell autophagy.	[98]
		rMC-1, 293T	LC3Ⅱ↑, Atg3↑, Atg5-Atg12↑	Autophagy is caused by HG stress.	[100]

2.1 Diabetic Nephropathy

DN is one of the most severe microvascular complications in diabetic patients, which can cause kidney failure[68]. When renal cells are exposed to hypoxia, genotoxic damage, oxidative stress, and ER stress, autophagy are activated, which is crucial for cell survival[69]. When autophagy is suppressed, renal fibrosis is exacerbated in DN[70]. ATG5 and LC3B levels decreased in DN mouse renal tissue compared with wild type (WT) mice, which is consistent with the DN patients results[71]. P62 protein accumulation significantly increased in the glomeruli of diabetic patients accompanied by podocyte loss. Podocyte-specific autophagy-deficiency in diabetic rats also resulted in massive proteinuria and tubulointerstitial injury. Meanwhile, LC3 decreased and foot process structures were damaged in the podocytes of Atg5 knockout in HFD mice[72]. Evidence suggests that HG increased the number of GFP-LC3 puncta (LC3-PE associated with autophagosome membranes) in podocytes and promoted podocyte autophagy. Atg5 deficiency in podocytes led to diabetic podocyte disease, accompanied by glomerular filtration barrier injury and glomerular sclerosis[73]. Proximal tubule-specific Atg7 knockout resulted in autophagy deficiency in diabetic mice and aggravated renal hypertrophy, tubular injury, inflammation, fibrosis, and proteinuria, suggesting the development of serious hypertrophy in diabetic kidneys when tubular autophagy was suppressed[74]. HG activates the JAK/STAT pathway to inhibit autophagy in mice, thereby aggravating the DN progression[75]. Lysosome depletion promotes autophagy dysregulation and accelerates tubular epithelial cells injury under diabetic conditions[76]. Autophagy in DN was inhibited by p-AMPK reduction and p-mTOR activation, so that autophagy is activated in the DN treatment in this pathway[77]. The expression of E-cadherin and LC3 proteins was upregulated and the expression of P62, p-mTOR, p-Akt, and PI3K was downregulated in DN rats and MPC5 cells, indicating that autophagy is enhanced, which effectively protected kidney function[78, 79]. All of these studies indicate that autophagy activation is positive for DN or its therapies.

2.2 Diabetic Central Neuropathy

In diabetic neuropathy's early stage, mitochondria are divided and neuronal cells are damaged. The expression levels of Aβ and p-Tau were increased in the brain of streptozotocin (STZ)-induced diabetic rats, and the ratio of LC3 Ⅱ/LC3 Ⅰ and the expression of Beclin1 in the brain were decreased. Results were consistent with those of neurons cultured in HG condition *in vitro*. Therefore, diabetes enhances the pathological progression of Alzheimer's disease (AD) and neuronal autophagy was directly inhibited in diabetes[80]. Autophagy activation protected neurons from abnormal metabolism. Pretreatment with rapamycin in PC12 cells cultured with oleic acid upregulated the expression of LC3 Ⅱ and reduced the death of PC12 cells caused by lipotoxicity[81]. Autophagy was induced by diabetes, but autophagy inhibition aggravates apoptosis of hippocampal primary neurons cultured with HG[82]. High-mobility group box 1 (HMGB1) is a key factor in regulating the apoptosis and autophagy of hippocampal neurons in DM. *In vitro*, transfection of HMGB1 siRNA into HT22 cells enhanced autophagy and reversed neuronal apoptosis[24]. After autophagy inhibitor 3-medthyladenine (3-MA) treatment in STZ-induced diabetic mice, the long non-coding RNA PVT1 expression increased, LC3 Ⅱ/LC3 Ⅰ ratio decreased, Beclin1 expression decreased, and cell apoptosis increased by HE staining. It is indicated that PVT1 negatively regulated autophagy to protect hippocampal neuron apoptosis and improved the cognitive dysfunction of diabetic mice[83]. Also, 3-MA treatment significantly increased the p-Tau levels and pmTOR[84]. Autophagy is activated through the AMPK/mTOR pathway with increased AMPK phosphorylation and decreased mTOR phosphorylation, which has a protective effect on the dysfunction of hippocampal neurons and cognition caused by diabetes[85, 86]. Generally, autophagy plays a protective role in the diabetic neuropathy process.

2.3 Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DC) is a ventricular dysfunction that occurs in diabetic patients and is associated with cardiac autophagy, damage of mitochondrial structure and dysfunction inhibition[87]. T2DM rats showed left ventricular dysfunction, increased cardiomyocyte apoptosis, and reduced cardiac autophagy. However, ERK and P38 MAPK phosphorylation inhibition and LC3-Ⅱ, Atg5, and Atg7 expression increase restored cardiac autophagy, which ameliorate IR and reduce cardiomyocyte apoptosis[88]. SIRT3 knockout mice with STZ-induced diabetes suffered from cardiac dysfunction, interstitial fibrosis, cardiomyocyte apoptosis, and mitochondrial damage, which inhibited mitochondrial autophagy. SIRT3 overexpression *in vitro* activated mitochondrial autophagy to maintain mitochondrial homeostasis which inhibited cardiomyocyte apoptosis, indicating that SIRT3 positively regulated mitochondrial autophagy to prevent myocardial damage[89]. Cardiac autophagy was inhibited and myocardial cell apoptosis was increased in diabetic mice, which was promoted by activating AMPK and JNK1. B-cell lymphoma gene 2 (Bcl-2) and Bim were phosphorylated and their interaction with Beclin1 were damaged, so that apoptosis was halted and cardiac function was improved[90]. DC was alleviated by promoting autophagy[91]. HG inhibited autophagy in H9C2 cells and increased intracellular ROS content to result in mitochondrial membrane potential loss with increased p-mTOR expression that

promoted cell apoptosis. Autophagy was improved by AMPK/mTOR pathway inhibition to suppress cell apoptosis, which alleviated cardiac injury caused by glucose poisoning[92, 93].

2.4 Diabetic Retinopathy

Diabetic retinopathy (DR) is a serious complication of diabetes and a major cause of blindness[94]. Lysosomal damage and autophagy dysfunction are the early features of DR. MAPK3 expression downregulation and Atg16L1 expression upregulation may be potential biomarkers for DR diagnosis[95, 96]. Autophagy's degradative capacity declined in retinal pigment epithelial (RPE) cells upon exposure to HG. However, autophagy restoration improved RPE cells apoptosis in DR[97]. In *in vivo* DR models, lysosomal dysfunction and P62 accumulation increased, which promoted apoptosis of retinal Müller cells. Cell proliferation increased through enhancing autophagy[94, 98, 99]. Histone HIST1H1C overexpression upregulated the expression of histone deacetylase 1 to maintain the deacetylation state of histone H4K16, to increase binding of Atg5 to Atg12, which then upregulated Atg3 and Atg7 expression to promote autophagy of retinal cell lines[100]. After treatment with 3-MA, the retinal ganglion cell apoptosis increased[101]. Autophagy activator has therapeutic potential in DR treatment. For example, artesunate enhanced autophagy by activating AMPK/SIRT1 pathway to protect diabetic rats from retinal injury[102].

3 CONCLUSION AND PROSPECT

The role of autophagy in the development and complications of diabetes has been well explored. However, it remains unclear whether autophagy inhibits or promotes the progression of diabetes. Autophagy also has different effects on IR in different parts of the body. For instance, it has a positive protective effect on liver and skeletal muscles[51], but aggravates IR in adipose tissue[65]. In addition, age, sex or strain of animals may also affect autophagy activity detection in diabetes models. There is complex variability in different experiments, making it difficult to directly compare different studies.

It is clear that the key factor of autophagy is mTOR. Atgs is involved in the development of diabetes. Atgs or molecule regulation can reduce the damage of islet cells by free fatty acids, inflammation, HG, oxidation, and ER stress. This should delay the decline of islet function in diabetic patients. In the initial stage of autophagy, MAPK, AMPK, and other signaling pathways can activate autophagy[15, 17]. The binding of VAMP7 protein to Atg9 can promote autophagy-lysosomal fusion[19]. NO signal impairs lysosome function and affects autophagosomes degradation[56]. Therefore, active research and development of drugs to regulate autophagy as an intervention target are expected to become an important direction in diabetes treatment.

Autophagy is a dynamic process and the current information on static autophagy-related proteins cannot fully reflect the process of autophagy. It is not known whether autophagy is a key factor in disease progression. Screening active drugs that activate autophagy and elucidating its mechanism of action will be a breakthrough in diabetes treatment in the future. Despite autophagy treatment success *in vivo* and *in vitro*, further studies are still needed to verify the practical application in humans.

Conflict of Interest Statement

The authors declare no conflict of interest.

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